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Risk Factors and Chemical Composition of Urinary Stones in the Azorean Population (São Miguel Island - Portugal): A Preliminary Study

Fatores de Risco e Composição Química de Cálculos Urinários na População Açoriana (Ilha de São Miguel - Portugal): Um Estudo Preliminar

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Abstract

Introduction: *Urinary stone disease is one of the most common disorders of the urinary tract. However, the main risk factors and chemical composition of urinary stones in the population of the Azores are unknown. The objective of this study was to define the most important factors associated with the formation of urinary calculi, investigating eating habits, family history and chemical composition of the calculi in the population of the Azores.*

Methods: *The data were collected from 46 patients of the Hospital do Divino Espirito Santo and 48 healthy volunteers. A questionnaire was recorded on the medical and family history of the participants and on their life habits. The chemical composition of the calculi was evaluated by ICP-MS.*

Results: *It was observed that the study group has a higher prevalence of diabetes and cases of urinary calculi in the family compared to the reference group. A positive correlation was found between calcium in the stones and the contents of sodium, magnesium, zinc, molybdenum and strontium.*

Conclusion: *This study reveals that family history, diabetes and water consumption play an important role in the development of urinary calculi in the population of the Azores. The chemical content of the stones should also be considered since these data could help the medical community to understand the causes of urinary stone formation and adapt the medication and preventive measures to the patient and to the type of kidney stone produced.*

Keywords: Risk Factors; Urinary Calculi/chemistry.

Resumo

Introdução: A doença provocada pela formação de cálculos urinários é um dos distúrbios mais comuns do trato urinário. No entanto, os principais fatores de risco e composição química dos cálculos urinários na população dos Açores são desconhecidos. O objetivo deste estudo foi definir quais os fatores mais importantes associados à formação de cálculos urinários, investigar hábitos alimentares, história familiar e composição química dos cálculos na população dos Açores.

Métodos: Foram recolhidos dados de 46 pacientes do Hospital do Divino Espírito Santo e de 48 voluntários saudáveis. Aplicou-se um questionário referente a antecedentes médicos e familiares dos participantes e aos seus hábitos de vida. A composição química dos cálculos foi avaliada pelo ICP-MS.

Resultados: Observou-se que o grupo de estudo apresenta uma maior prevalência de diabetes e casos de cálculos urinários na família em comparação com o grupo de referência. Uma correlação positiva foi encontrada entre o cálcio existente nos cálculos e as concentrações de sódio, magnésio, zinco, molibdênio e estrôncio.

Conclusão: Este estudo revela que a história familiar, diabetes e o consumo de água desempenham um papel importante no desenvolvimento de cálculos urinários na população dos Açores. O conteúdo químico dos cálculos também deve ser considerado, pois esses dados podem ajudar a comunidade médica a compreender as causas da formação de cálculos urinários e adaptar a medicação e medidas preventivas ao paciente e ao tipo de cálculo urinário.

Palavras-chave: Cálculos Urinários/química; Factores de Risco.

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Introduction

The urinary stone disease (USD) is one of the most common disorders of the urinary tract.[1] The risk for urinary stone formation varies in different parts of the world, being higher in the western (9%, 12%, and 15% in Europe, Canada and USA, respectively) than in the eastern hemisphere (1% - 5%).[2] The incidence of USD is associated with epidemiologic and demographic factors such as age, gender, racial distribution, previous medical condition, socioeconomic class, family history and dietary habits.[3-4] In the European Union, the prevalence and incidence of the USD are increasing for the last two decades[5]: in Spain, the annual prevalence increased from 4.16% in 1986 to 5.06% in 2007[6,7]; and, in Germany increased from 4% to 4.7%, between 1979 and 2000.[8] In Portugal the information regarding the USD is scarce although according to Reis-Santos,[9] about 7% of the Portuguese population had at least one situation of renal colic. Regarding the Azores, a volcanic archipelago, the prevalence of USD is currently unknown, but is probably higher than the overall estimated prevalence in the Portuguese population.[10] This is hypothesized since in the Azores: i) the dietary habits include high protein and salt intakes and, more recently, a high consumption of carbonated beverage rich in fructose, ii) about 70% of the Azorean inhabitants have a sedentary lifestyle and are overweighed [according to the *Inquérito Nacional de Saúde com Exame Físico* (2015)] and, iii) the comorbidities, such as diabetes and hypertension, have a prevalence of 10% and 34%, respectively in the archipelago.

Considering that i) the risk of stone formation in an individual is estimated at 5% – 10%[11] with a recurrence rate as high as 50% at 5 years and, 80% – 90% in 10 years[12] and, ii) there are no reports for the disease pathogenesis or prevalence in the Azores, this study was developed in order to characterize the chemical profile of the urinary stones and to define the most important factors associated with its formation in the inhabitants of the São Miguel Island.

Material and Methods

STUDY POPULATION

This study was carried on São Miguel Island, the largest one of the Azores (Portugal) archipelago.

The study group comprised 46 patients hospitalized or followed in routine consultations at the Urology Department of the Hospital do Divino Espírito Santo (Ponta Delgada); both genders were considered and the age of the participants ranged between 24 and 84 years.

The reference group, with 48 participants with no USD medical history, was formed by matching age and gender with the study group. Each participant answered a questionnaire regarding information about demographic characteristics, dietary habits and associated health issues (summarized in Table 1).

The Ethics Board of Divino Espírito Santo Hospital (Ponta Delgada, Azores, Portugal) approved the study (S-HDES/2014/49). All individuals signed a written informed consent, in compliance with the Helsinki Declaration and Oviedo Convention, to participate in this study.

SAMPLE COLLECTION AND ANALYSIS

Forty-six stones of different types, including renal (34 samples), bladder (8 samples) and ureter (4 samples) stones were collected by surgical extraction or by spontaneous expulsion.

Stone opacity was characterized using x-ray; all the analyzed stones were radiopaque. Color and texture of each stone were evaluated (Online resource Table S1).

To determine the stones chemical composition, samples with a minimum weight of 0.2 g were sent to a certified laboratory for ICP-MS (Inductively Coupled Plasma Mass Spectrometry) examination. Since only 13 samples had the minimum weight required, only two groups were considered according to its calcium content: <5% [0.02% - 1.99%] (low calcium stones) and ≥ 15% [17.2% - 22.6%] (high calcium stones).

STATISTICAL ANALYSIS

T-test was used to compare the age and the weight between the studied groups, while for the remaining continuous variables the Mann-Whitney *U*-test was used.

Pearson chi-square test was used to compare the reference and study groups regarding gender (male *versus* female), the prevalence of diabetes (yes *versus* no) and of hypertension (yes *versus* no), eating habits, such as the use of salt in meal preparation (yes *versus* no) and chocolate daily consumption (yes *versus* no) and, the presence of recurring cases of urinary stones in the family (yes *versus* no).

The elemental characterization of the urinary stones was compared by Mann-Whitney *U*-test. For the significant chemical elements, Spearman correlation was used to test the association between calcium percentage and the element concentration in the urinary stones. All statistical analysis was performed using IBM SPSS Statistics 20.0 for Windows, with statistical significance set at $p \leq 0.05$.

Results

Table 1 presents the general description of the studied groups. Reference and study groups are similar in age, gender, weight and height. Both groups have a similar consumption of tap water, salt and chocolate, but differ significantly in the consumption of bottled water, meat and fish: individuals in the study group drink more bottled water (4.41 ± 0.48 *vs* 2.77 ± 0.35 cups of water/ day); on the other hand, the reference group presents a higher consumption of meat (3.38 ± 0.29 *vs* 2.59 ± 0.21 nº meals/week) and fish (4.13 ± 0.31 *vs* 2.89 ± 0.28 nº meals/week). The prevalence of diabetes in the study group is significantly higher (20%) than in the reference one (4%). Also, the study group has a significantly higher prevalence of urinary stone cases in the family (57% vs 25%) and, a significantly higher rate of USD recurrence in the family (70% *vs* 42%).

URINARY STONES CHEMICAL COMPOSITION

Table 2 shows the general chemical composition of the urinary

Table 1: Description of the studied populations: reference group (with no USD) and study group (with USD) [mean ± SE for continuous variables or n (%) for categorical variables]

Characteristic	Reference group (n=48)	Study group (n=46)	*p*-value[a]
General characteristics			
Age[b]	50.7 ± 2.11	49.7 ± 2.18	0.756
Gender, male	23 (47.9)	29 (63)	0.140
Weight (kg)	74.3 ± 1.9	78.6 ± 2.5	0.291
Height (cm)	167 ± 0.01	167 ± 0.01	0.889
Dietary habits			
Drinking tap water[c]	3.44 ± 0.42	2.74 ± 0.41	0.212
Drinking bottled water[c]	2.77 ± 0.35	4.41 ± 0.48	0.009
Meals, meat[d]	3.38 ± 0.29	2.59 ± 0.21	0.043
Meals, fish[d]	4.13 ± 0.31	2.89 ± 0.28	0.003
Salt in meals, yes	12 (25)	17 (37)	0.210
Eats chocolate, yes	18 (38)	21 (46)	0.423
Associated Diseases			
Hypertension, yes	12 (25)	15 (33)	0.415
Diabetes, yes	2 (4)	9 (20)	0.020
Study characteristics			
Cases in family, yes	12 (25)	20 (57)	0.047
Recurrence, yes	5 (42)	14 (70)	0.015

[a]*t*- test (age and weight); Mann-Whitney U-test (other continuous variables); χ^2 test (for categorical variables).
[b]Age is represented in years.
[c]Water drinking is expressed in cups per day.
[d]Meals of meat and fish are represented in number of meals per week.

stones. About 62% of the stones were composed predominantly of calcium compounds (high calcium content) and the remaining 38% presented low calcium content (< 5% of calcium).

The studied stone groups have a similar chemical content for most of the analyzed elements, only differing in the following nine elements: Na, Mg, Ca, Fe, Ni, Co, Zn, Mo, Sr and Pb (Table 2). The calcium content in the urinary stones was strongly and positively correlated with the content of Na (rs = 0.721, p = 0.005), Mg (r_s = 0.839, p < 0.001), Zn (r_s = 0.933, p < 0.001), Mo (r_s = 0.828, p < 0.001) and Sr (r_s = 0.829, p < 0.001) (Table 3).

Discussion

Results demonstrate that patients with urinary stones consumed more bottled water than healthy subjects, but no significant differences were observed in the consumption of tap water. This may be because patients with urinary stones are routinely advised to increase their fluid intake in order to decrease the risk of stone recurrence, and therefore bottled water appears to be a better way to ensure the uptake of the recommended water during the day. Also, when drinking bottled water, patients have a more accurate perception of the total amount of water consumed. In any case, the consumption of

Table 2: Elemental composition (mean ± SE) of the urinary stones from the study population, considering a group of stones with low calcium content (< 5%) and a group with high calcium content (≥ 15%)

Chemical elements	Low calcium content (n= 5)	High calcium content (n=8)	*p*-value[a]
%			
Na	0.06 ± 0.01	0.26 ± 0.07	0.006
Mg	0.004 ± 0.002	0.37 ± 0.29	0.002
Al	0.09 ± 0.05	0.13 ± 0.03	0.171
K	0.04 ± 0.006	0.75 ± 0.02	0.093
Ca	0.84 ± 0.42	19.4 ± 0.68	0.002
Fe	0.05 ± 0.03	0.21 ± 0.03	0.030
ppm			
B	4.60 ± 1.33	2.38 ± 0.78	0.171
Li	0.20 ± 0.20	0.64 ± 0.16	0.171
V	1.60 ± 0.24	1.88 ± 0.23	0.524
Cr	7.0 ± 1.28	11.2 ± 1.72	0.065
Mn	21 ± 4.94	29 ± 3.57	0.354
Ni	1.14 ± 0.97	5.66 ± 1.70	0.045
Co	0.06 ± 0.06	0.36 ± 0.10	0.030
Bi	0.04 ± 0.006	0.04 ± 0.003	0.724
Se	0.16 ± 0.07	0.11 ± 0.07	0.622
Zn	16.4 ± 10.1	357 ± 99.1	0.003
Ga	0.30 ± 0.08	0.43 ± 0.08	0.221
As	0.18 ± 0.18	0.86 ± 0.05	0.284
Rb	1.00 ± 0.11	2.38 ± 1.23	0.724
Mo	0.33 ± 0.06	0.66 ± 0.08	0.019
Sn	0.40 ± 0.24	1.10 ± 0.13	0.065
Ba	4.40 ± 4.15	1.88 ± 0.55	0.284
Cu	6.92 ± 1.88	8.08 ± 2.66	0.724
Sr	2.12 ± 0.91	42.0 ± 8.70	0.002
W	0.16 ± 0.05	0.29 ± 0.07	0.354
Ti	0.11 ± 0.05	0.90 ± 0.72	1.00
Pb	0.96 ± 0.42	12.2 ± 4.14	0.011
ppb			
Hg	138 ± 59	130 ± 37	1.00

[a]Mann-Whitney *U*-test.

bottled water should be monitored with particular attention, regarding the brand of the water consumed since there are several brands of water with different concentrations of sodium (see supplementary material, Table S2). It is appropriate to recommend not only the increase in consumption of water but also, the study of the labeling of the available brands to

Table 3: Correlation between calcium (%) in urinary stones and sodium and magnesium (%), zinc, molybdenum and strontium (ppm) in the study group

Chemical elements	Spearman correlation	Sig. (2-tailed)
Calcium (Ca) *vs* Sodium (Na)	0.721**	0.005
Calcium (Ca) *vs* Magnesium(Mg)	0.839**	<0.001
Calcium (Ca) *vs* Zinc (Zn)	0.933**	<0.001
Calcium (Ca) *vs* Molybdenum (Mo)	0.828**	<0.001
Calcium (Ca) *vs* Strontium (Sr)	0.829**	<0.001

**Spearman's correlation is significant at *p*=0.01

choose the one with the lowest sodium content since the consumption of high concentrations of sodium allows the increase of the excretion of calcium and potassium along with citrate, resulting in a change in urinary pH that will eventually increase the risk of stone formation.[13]

Another dietary habit recognized to increase the chances of developing urinary stones is the consumption of animal protein that may cause the body to release more calcium, uric acid and citrate in the urine, particularly in diets with high protein content (> 2.0 g/kg/d).[14] Although such trend was not observed in this study (the daily intake of protein -meat and fish in the study group is 0.48 g/kg/d while in the reference is 0.69 g/kg/d), it must be taken in consideration that dietary intake was only assessed on one moment, which may not accurately reflect the participants' long-term food and nutrient intake. Also, the used questionnaire did not consider the dietary intake of fresh fruit and fibres, food resources that may reduce the risk of urinary stone formation.[15,16] Regarding the chocolate consumption, though no significant differences were observed, the study group had a slightly higher consumption rate. According to Robertson,[17] chocolate consumption can increase the risk of formation of urinary stones, since it can rapidly increase the urinary oxalate resulting in the formation of abnormal crystals and agglomerates of calcium oxalate that is the most important risk factor for calcium oxalate stone formation.

Type 2 diabetes mellitus (DM) is considered a risk factor for uric-acid urinary stone formation mainly because diabetic patients have highly acidic urine.[18] Polat *et al*,[19] in a retrospective study from 2008 to 2015, showed that diabetes was significantly related to the risk of developing calcium stones. Therefore, our results were according to the expected regarding the association between patients with urinary stones and diabetes.

In our study, a patient with urinary stones is twice as likely as a healthy subject to have at least one first degree relative with urinary stones (57% *vs* 25%). Similar results were recently described by Sofia *et al*[20] in a study where family history is significantly associated with urinary stone formation and recurrence.

Considering the chemical composition of the analyzed calculi, as expected calcium is the main constituent in most of the stones, since it is considered in most countries over the world as the more common and most abundant component of urinary stones.[21] Calcium oxalate stones are described as the main type of urinary calculi in western countries and account for at least 70% of all kidney stones; in our study the rate of stones with high content in calcium was 62%. Considering the chemical analysis, the global amount of metals (Na, Mg, Fe, Ni, Co, Zn, Mo, Sr and Pb) was significantly greater in the high content calcium stones than in the low calcium stones. Similarly, to the observed in other studies,[22] the highest metal contents in calcium stones were for Zn, followed by Sr. The observed differences in the metal contents between both stone groups may be related with the similarity between the ion charge and size of Zn and Sr and calcium, which allows these elements to substitute calcium in the crystal lattice.[23] Therefore, Zn and Sr are more likely to incorporate into calcium-containing stones, which is revealed by the strong and positive correlation between calcium and these two elements, observed in this study. A strong and positive correlation was also found between the calcium content and Na and Mo. Again, such association was also observed in previous studies.[24,25] Although magnesium is recognized to inhibit crystal formation, thus reducing the risk for forming urinary stones, a positive correlation was found between Ca and Mg contents.

Although urine and blood biochemistry were not considered in this study, since the participants with spontaneous expulsion didn't undergo these additional analysis, both

Online resource
Table S1: Characterization of the surface of the urinary stones

Type	Sub-type	Main component	Characteristics	% of stones
I	Ia	Whewellite	Mulberry stone with sharp projections.	3.03%
I	Ib	Whewellite	Rough texture, color brown to dark brown.	27.27%
I	Ic	Whewellite	Rough texture, color brown to dark brown.	3.03%
I	Ie	Whewellite	Localized budding, rough texture.	18.18%
II	IIa	Weddellite	Spiculated texture with bipyramidal aggregations of crystals with sharp angle.	15.15%
II	IIb	Weddellite ± Whewellite	Spiculated texture with bipyramidal aggregations of crystals.	9.09%
V	Va	Cystine	Smal, round and smooth.	12.12%
VI	VIb	Proteins	Heterogeneous, irregular and rough texture.	12.12%

* The criteria used to assess the type, subtype, main component and general characteristics of the urinary stone was based in Daundon and Jungers[27]

Online resource
Table S2: Characterization of mineral composition in bottled water

Brand	Mineralization (mg/L)	Bicarbonate (mg/L)	Chloride (mg/L)	Calcium (mg/L)	Magnesium (mg/L)	Sodium (mg/L)
A	103	38.7	9	6.2	1.6	12.9
B	86	26.6	5.2	2.7	1.7	11.3
C	39	16.5	3.2	2.7	n.d	4.4
D	31	6.7	2.2	0.7	0.3	3.5
E	49	13	9	0.74	1.7	7.3
F	45	5.1	8	0.8	0.5	6.2
G	40	13.2	6,8	2.2	2.3	4.7
H	90	26.9	8.4	7.3	n.d	10.6

should be considered in future studies in order to help identifying metabolic disorders and to provide accurate information on a possible metabolic disease or risk factors involved in lithogenesis.[26]

These results highlight the necessity of the development of studies that can provide better insights regarding the role of these elements in stone formation or their use as useful indicators (biomarkers) for medical treatments and/or prevention measures.

Conclusion

This study revealed that family history, associated diseases, such as diabetes, and some eating habits play a major role in the development of urinary stones in the Azorean population. Therefore, a dietary intervention on a large scale and health education in this regard may be helpful in preventing the development of urinary stone formation in the Azores.

Also, it seems clear that the evaluation of the elemental content in different types of stones should always be considered along with their mineralogical composition, since this data could assist the medical community to understand the causes of the formation of urinary stones and lead to the development of an adequate method to avoid or diminish the probability of urinary stone formation.

Ethical Disclosures

Conflicts of Interest: This study had the financial support of Bio-Air-Biomonitoring air pollution: development of an integrated system (M2.1.2/F/00872011) from Fundo Regional da Ciência (Regional Government of the Azores) (PROEMPREGO Programme).

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Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Responsabilidades Éticas

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Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação dos dados de doentes.

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